REMARKS

Applicants note that the Office Action is indicated as a first action and final, because "[a]ll claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application." *See* Office Action, page 5.

Applicants submit herewith a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114, thus withdrawing finality of the Office Action dated March 4, 2005. With the submitted RCE, Applicants also request entry of the claim amendments and new claims.

As noted in the Office Action Summary, claims 1-7 and 22-29 stand canceled, and claims 8-11 and 21 are pending. After entry of the instant Reply and Amendment, claims 8-11, 21, and 30-35 will be pending.

Applicants introduce new claims 30-35. The new claims are directed to a method for treatment of chronic cardiac dysfunction. The new claims are supported by the specification in the claims as originally filed, and in the specification at least at page 1, lines 6-11, page 3, lines 15-24, page 20, line 37 to page 22, line 2, and in the examples generally. The amendments to claims 8-10 are supported in the specification at least at page 6, line 34 to page 7, line 5.

I. Rejection under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 8-11 and 21 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification purportedly lacks an enabling disclosure. The Office admits that the treatment of cardiac hypertrophy is enabled for treatment in rats. However, the Office alleges that the specification does not provide enablement for "(1) treatment of cardiac hypertrophy with ANP in any species other than rats at dosages which do not cause diuretic and hypotensive effects; (2) treatment of cardiac hypertrophy with agents other than ANP at dosages which do not cause diuretic and hypotensive effects." *See* Office Action dated March 4, 2005, page 2.

Applicants respectfully traverse the rejection. The burden of setting forth a case of lack of enablement is on the Office. *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). The case law makes clear that properly reasoned and supported statements explaining any failure to comply with Section 112 are a requirement to support a rejection. *Wright*, 27 U.S.P.Q.2d at 1513. The *35 U.S.C. § 112 First Paragraph Enablement Training* Manual, also stresses that Examiners must set forth a proper analysis of the *Wands* factors. It is improper to conclude that disclosure is not enabling based on analysis of only one of the

Wands factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence ***as a whole***. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 and 1407 (Fed. Cir. 1988). Applicants submit that a *prima facie* case has not been evinced.

Applicants first submit that a reasoned analysis of the *Wands* factors was not provided in the Office Action dated March 4, 2005. Therefore, no *prima facie* case supporting lack of enablement was set forth.

Second, Applicants submit that no working examples are required in any application, because applications can themselves be a constructive reduction to practice. Applicants provide working examples in the specification with *in vivo* rat data. The issue is whether the rat data can correlate to outcomes in other mammals. The Office must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the method claimed. *See Training Materials For Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph – Enablement Chemical/Biotechnical Applications,* page 28. Correlation of the data would have been reasonable at the time given the teachings of the instant specification and what was known in the art at the time. Arguments for correlating the data are provided below.

Regarding the reference of Blaine (U.S. Pat. No. 4,652,549), it is being cited out of context. In the "Background of the Invention" section of Blaine, it is discussed that partially purified and crude extracts were shown to have diuretic effects. It is unknown what these crude and partially purified extracts contained to which the potent diuretic effect is attributable. Blaine goes on to discuss that the active agents were atrial natriuretic factor (ANF). Whether the ANFs had potent diuretic effects is not explicitly discussed; the crude extracts are discussed as having diuretic effect only at col. 1, lines 21-22. Therefore, to clarify the record, Blaine is improperly described.

The Office goes on to state that Applicants argued in their response dated July 25, 2002 that "the finding of the effect of ANP without involving hypotensive and diuretic effect is unexpected and unusual." Applicants have reviewed the cited response and cannot find where in the response the Office is referring. As such, Applicants cannot respond.

The Office then follows with the statement that "the examiner has reasons to believe that effect of the same agent, namely ANP, might be different in different species, and maintains that since the art is deemed unpredictable in regard to ANP acting without

involving hypotensive and diuretic effects, and in the absence or working examples and sufficient guidance, specification does not commensurate with the scope of invention claimed." Page 3, Office Action. This conclusion does not logically follow the reasons provided in the subject paragraph. Applicants have provided *in vivo* working examples with the rat model. Also, as discussed below in the analysis of the Squadrito et al. reference, there is significant conservation of ANP sequences across mammals. The Office does not provide substantive scientific evidence or reasoning to show that a skilled artisan would have viewed the claimed subject matter as unpredictable. The Office only states a conclusion without the requisite support for its conclusion. If the Office indeed has reasons to believe that the effect is different, Applicants request that the Office provide scientific references to supports its "reasons," or that the Office take Official Notice of its reasons. *See* M.P.E.P. § 2144.03.

The last paragraph on page 3 of the Office Action purportedly is directed to the second part of the rejection (*i.e.*, "(2) treatment of cardiac hypertrophy with agents other than ANP at dosages which do not cause diuretic and hypotensive effects."). As discussed *supra*, Blaine only discusses a diuretic effect with crude extracts. Blaine discusses a decrease in water content as occurring by ANP administration. However, an increase in water content does not cause cardiac hypertrophy. Therefore, the office is making an unsupported conclusion regarding the data discussed in Blaine – Blaine does not support this conclusion.

Applicants' specification lists brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) as active substances for the treatment of cardiac hypertrophy. Both ANP and BNP exhibit various biological activities, including natriuretic and hypotensive effects through a common receptor, guanylyl cyclase A (GC-A). To date, no receptor other than GC-A for ANP and BNP has been identified in mammals.

It has been reported that both human ANP and human BNP similarly exhibit improved blood stream dynamics, natriuretic action, and hormone secretion at the same dose, *i.e.*, 0.1 μg/kg/min, when they are administered to a patient with acute cardiac dysfunction. *See* Saito et al., *Circulation* 76: 115-124 (1987). Thus, it would have been reasonable to expect at the time that human BNP, like human ANP, would similarly exhibit inhibitory action to cardiac hypertrophy if administered at a low dose.

Given that there is conservation of the ANP sequences and that both human ANP and human BNP work through a common receptor, and yield common responses, an artisan of ordinary skill would have concluded at the time that the application is enabled for agents other than ANP.

The Squadrito et al. Reference

The Office further asserted that the Squadrito et al. (Database Medline, PubMed ID: 2473344, 1989, Abstract only) reference allegedly demonstrates differences in effects of ANP species derived from different sources. The Office goes on to state that the issue "is not the similarity of known effects between various natriuretic peptide receptor ligands, but whether these different ligands will be capable of acting without causing diuretic and hypotensive effects."

Applicants respectfully disagree with the Office's position. First, the structure of ANP is well conserved between different animal species. For example, the amino acid sequence of human ANP differs from the rat sequence by one residue of the 28 residues (*i.e.*, residue 12 is a methionine in human and is an isoleucine in the rat protein). *See* Kangawa et al., *BBRC* 118: 131-139 (1984); and Kangawa et al., *BBRC* 121: 585-591 (1984). The structure of mouse and rabbit ANP is the same as that of rat ANP, and the structure of dog and pig ANP is the same as human ANP (*see*, Oikawa et al., *BBRC* 132: 892-899 (1985) and Forssmann et al., *Cell Tissue Res.*, 238: 425-430 (1984)). Therefore, there is a high degree of conservation between different mammalian ANPs.

Second, human ANP exhibits strong natriuretic effect in rats. *See* Kangawa et al.. *BBRC* 118: 131-139 (1984). The observed activity of human ANP in rats is not substantially different from that of rat ANP. Moreover, human ANP and rat ANP have substantially the same chicken colon relaxation activity and rat arterial relaxation activity (Minamitake et al., *Peptide Chemistry*, pp. 229-231 (ed. N. Izumiya, 1984); and T. Watanabe et al., *Eur. J. Pharmacol.* 147: 49-57 (1988)). Additionally, if the twelfth position of ANP has a hydrophobic amino acid such as Met, Ile, Nle, etc., there was no substantial change in activity. Watanabe et al., *Eur. J. Pharmacol.* 147: 49-57 (1988).

The fact that human ANP when administered to rats does not induce the same effect as rat ANP (*i.e.*, modify mean arterial pressure, heart rate, and water intake) is not dispositive of the agents being able to act without causing diuretic and hypotensive effects in animal appropriate models (*i.e.*, rat ANP in rat and human ANP in humans). When the Squadrito reference is viewed ***as a whole*** in view of the references discussed above and Applicants' specification, a skilled artisan would have concluded at the time that rat ANP enables the use of other ANPs in other species.

Thus, with regard to the reference of Squadrito et al., Applicants submit that the Office has not adduced a scientifically supported *prima facie* case of lack of enablement. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Therefore, the references asserted by the Office do not evince a showing of lack of enablement. Additionally, in view of the sequence similarity and the similar activities of the polypeptides across species, and the various assays known at the time for testing compounds, Applicants submit that the specification provides sufficient enabling disclosure to carry on the claimed invention. Thus, one of skill in the art would recognize that it is sufficiently reasonable to apply information obtained in rats to humans or any other mammal.

II. Rejection under 35 U.S.C. § 102

Claims 8-11 and 21 stand rejected as purportedly anticipated by Blaine (U.S. Pat. No. 4,652,549) as evidenced by E. Espiner (*Curr. Opin. Endocrinol. & Diabetes* 5: 205-210).

Applicants respectfully traverse the rejection. "Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claims". *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 U.S.P.Q. 253, 256 (Fed. Cir. 1985). Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *Ex parte Skinner,* 2 U.S.P.Q.2d 1788, 1789 (Bd. Of Pat. Appeals & Int. 1987). The disclosure must be sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function. *See In re Oelrich*, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

There is no reference in Blaine that describes the treatment of a chronic cardiac dysfunction. Blaine does not teach or suggest treatment of a cardiac dysfunction that produces pulmonary congestion. In fact, Blaine does not discuss pulmonary congestion whatsoever. Additionally, Blaine does not teach or suggest a method of decreasing heart weight or a method of recession of cardiac hypertrophy after the cardiac hypertrophy has been established. Pulmonary congestion is also known as pulmonary edema. Pulmonary edema is usually caused by heart failure that results in increased pressure in the pulmonary (lung) veins. However, problems within the lungs themselves can also result in fluid accumulation. Pulmonary edema can be a complication of a heart attack (not considered to

be a chronic cardiac dysfunction), leaking or narrowed heart valves (mitral or aortic valves), or any disease of the heart that either results in weakening and/or stiffening of the heart muscle (cardiomyopathy). The failing heart transmits its increased pressure to the lung veins. As pressure in the lung veins rises, fluid is pushed into the air spaces (alveoli). This fluid then becomes a barrier to normal oxygen exchange, resulting in shortness of breath. Pulmonary edema can also be caused by direct lung injury from toxins including heat and poisonous gas, severe infection, or an excess of body fluid as seen in kidney failure. *See* (Internet:<http://health.allrefer.com/health/pulmonary-edema-info.html>) and attached print out thereof.

Additionally, Blaine does not teach or suggest that a compound that will act on guanylyl cyclase A (GC-A) natriuretic peptide receptor and accelerate production of cyclic guanosine monophosphate will reduce pulmonary congestion. As there is no suggestion, let along a teaching in this regard, there can be no expectation that the result may occur. There must be evidence to show that the result must occur, and not a mere possibility in the realm of possibilities.

In the June 3, 2004 Office Action, the Office asserts that "as pulmonary congestion arises from cardiac hypertrophy, treatment of the latter will also treat the former." This assertion is incorrect. The claims in this instance are directed to the treatment of pulmonary congestion arising from cardiac hypertrophy, and not another source. If the pulmonary congestion was caused by a toxin, for example, treatment of cardiac hypertrophy would not treat pulmonary congestion.

Espinar is cited for the teaching that it was allegedly "well known that ANF, as well as its analogs, stimulate guanylate cyclase A and production of cGMP". *See* page 6, Office Action dated June 3, 2004. This reference is admitted by the Patent Office to have been published after the filing date of the instant application. *See* page 4, Office Action dated June 3, 2004, fn. 1. Yet, Espinar is cited in the reference that it allegedly was "well known that ANF, as well as its analogs, stimulate guanylate cyclase A and production of cGMP." *Id.*, at page 6. The Office does not support its assertion of how it was well known in the art prior to the priority date of the instant application, given that it is using a reference published after the priority date of the instant application. Additionally, Espinar does not teach or suggest a method of decreasing heart weight or a method of recession of cardiac hypertrophy after the cardiac hypertrophy has been established. Only one reference can be used for a

rejection under 35 U.S.C. § 102, unless the second reference is used to show (1) an enabling disclosure, (2) explain the meaning of a term, or (3) show a characteristic not cannot be used to support Blaine, given the failings of Blaine. Therefore, Espinar is irrelevant

As the Blaine reference does not suggest or teach the claimed methods because all the limitations are not set forth by the reference, the reference does not anticipate the claims. Applicants therefore respectfully request withdrawal of the rejection and allowance of the claims.

CONCLUSION

In view of the foregoing, Applicants respectfully request the entry of the amendments to place the application in condition for allowance, or in the alternative, in better form for appeal.

If there are any other fees due in connection with the filing of this response, please charge the fees to Deposit Account No. 50-0573. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above or in the attached papers, such an extension is requested and the fee should also be charged to our Deposit Account.

If any matters remain outstanding, the Examiner is invited to contact the undersigned representative regarding this matter.

Respectfully submitted,
DRINKER, BIDDLE & REATH LLP

Date: September 6, 2005

By: _____
Mercedes K. Meyer, Ph.D., Esq.
Registration No. 44,939

1500 K Street, N.W., Suite 1100
Washington, D.C. 20005-1209
T: 202-842-8821
F: 202-842-8465